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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/227,854	01/11/1999	JIAN NI	PF210D1	7606

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HUMAN GENOME SCIENCES INC
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EXAMINER

BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
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1646

DATE MAILED: 09/22/2003

LL

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/227,854

Applicant(s)

NI ET AL.

Examiner

Michael Brannock

Art Unit

1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 17 April 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 35-54 and 60-70 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) 35-54 is/are allowed.
- 6) ☐ Claim(s) 60-70 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Status of Application: Claims and Amendments

Applicant is notified that the finality of the previous Office Action (Paper 15, 1/29/03) is withdrawn so that the basis of the rejections under 35 U.S.C. 112, first paragraph, can be more fully explained.

It is noted that a Notice of Appeal has been filed. Applicant can request a refund for the associated fees or leave it as credit for future appeals.

Applicant is notified that the amendments put forth in Paper 17, 7/3/02, have been entered in full. Claims 35-54 and 60-70 are pending and currently under examination.

Applicant is notified that the Declaration under 37 CFR 1.131, submitted as Paper 21, 4/21/03, is sufficient to preclude a rejection of the instant claims based on U.S. Patent No: 6313267, as was anticipated in the interview of October 21, 2002 (Paper 19).

Withdrawn Rejections:

Applicant is notified that any rejection of record that is not expressly maintained in this Office action has been withdrawn.

The rejection of claims 35-54 under 35 U.S.C. 112, first paragraph, as failing to be supported by an adequate scope of enabling disclosure is withdrawn. The claims are directed polypeptides *consisting* of fragments of the disclosed sequence that may or may not contain additional heterologous sequences. It is well established that such polypeptides are useful for

Art Unit: 1646

raising antibodies to the native protein, and as such, the scope of the claims is adequately supported by the disclosure.

Maintained Rejections:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 60-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polypeptides *consisting* of portions of SEQ ID NO: 2 that may or may not also include heterologous sequences, does not reasonably provide enablement for a genus of polypeptides that *comprise* only portions of SEQ ID NO: 2 or have a recited identity with SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims encompass polypeptide variants of the polypeptide of SEQ ID NO: 2, i.e. substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 2; yet the specification has not provided sufficient guidance as to how to make and use polypeptides which are not 100% identical to the polypeptide of SEQ ID NO: 2, but which still retain a desired property of the polypeptide of SEQ ID NO: 2. The claims require polypeptides comprising only portions of SEQ ID NO: 2, e.g. those comprising only 30 consecutive amino acids in the

Art Unit: 1646

sequence of SEQ ID NO: 2. No specific information is provided regarding the positions or identities of the remaining amino acids, which may make-up the greater portions of the claimed proteins. The claims also require polypeptides having a recited degree of identity with SEQ ID NO: 2. Thus, the vast majority of polypeptides being claimed are amino acid sequence variants of SEQ ID NO: 2, i.e. amino acid substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 2, yet the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make. Furthermore, the specification has not provided guidance as to what properties of the allelic variants or sequence variants of the protein corresponding to SEQ ID NO: 2 might be desired nor any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property. Applicant has not defined a difference in structure or difference in function between the protein corresponding to SEQ ID NO: 2 and variants of said protein. If a variant of the protein corresponding to SEQ ID NO: 2 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 2, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 2. Conversely, if a protein variant of SEQ ID NO: 2 need not have a disclosed property, the specification has failed to teach how to use such a variant.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the

Art Unit: 1646

sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). However, the specification has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Also, these or other regions may be critical determinants of antigenicity. It is well appreciated in the art of antibody production that it is unpredictable which amino acids are critical antigenic determinants (see Alexander et al., Proc. Natl. Acad. Sci. 89(3352-3356)1992. Protein antigenicity can be significantly reduced by substitution of even a single residue. Further, even if an amino acid substitution does not destroy the activity of the immunizing protein, the substitution may significantly reduce the antigenicity of the protein (see the Abstract of Alexander et al.). The specification does not provide sufficient guidance as to how to make antibodies that are specific to variants of SEQ ID NO: 2 that can be used for any specific purpose. The specification has not provided guidance as to natural variants that may exist, nor how to use antibodies specific to variants that might be created.

Although the specification outlines art-recognized procedures for producing variants (e.g. pages 13-14), this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the

Art Unit: 1646

specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Due to the large quantity of experimentation necessary to generate the infinite number of variant recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicant's arguments, presented in Paper 17 (7/3/02), have largely been addressed previously. Specifically, Applicant's assertions that it is routine in the art to search for amino acid sequence variants of proteins, based on Ikeda et al., and Stuurman et al., are not persuasive. Each of the references teach an extensive research plan to randomly make and test polypeptide variants. As stated above, although the specification does provide for methods of making and testing mutants for activity, this invitation to perform essentially random trial and error experimentation to try to find active variants is unduly burdensome. Specific, not general, teachings are required, yet none are given.

Additionally, it must be pointed out that the scale of mutagenesis attempted by Ikeda et al., and by Stuurman et al., is astronomically smaller than the scope of what is instantly being

Art Unit: 1646

claimed. Ikeda et al. worked with single and sometimes double or triple mutations in a protein that is approximately 360 residues in length (see col 2 of page 6294); this is (at most) less than a 1% change in amino acid sequence. Similarly, Stuurman et al. studied single amino acid changes (see col 2 of page 3141). Thus, the skilled artisan would not accept that the teachings of Ikeda et al., and by Stuurman et al. support the concept that specification, without any meaningful specific information, would be enabling for that which is claimed.

Claims 60-70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses a polypeptide of SEQ ID NO: 2, yet the claims encompass polypeptides not described in the specification, i.e. proteins which comprise only portions of SEQ ID NO: 2, e.g. sequences from other species, mutated sequences, allelic variants, or sequences that have a recited degree of identity. None of these sequences meet the written description provision of 35 U.S.C. 112, first paragraph. Although one of skill in the art would reasonably predict that these sequences exist, one would not be able make useful predictions as to the amino acid positions or identities of those sequences based on the information disclosed in the specification.

The instant disclosure of a single polypeptide, that of SEQ ID NO: 2, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of*

Art Unit: 1646

the University of California v Eli Lilly & Co, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polypeptide sequence SEQ ID NO: 2, which is not sufficient to describe the essentially limitless genera encompassed by the claims.

The instant claims are not directed to that which is disclosed as essential to the invention, i.e. something that is homologous to the parent SEQ ID NO: 2 and has the function the parent protein. Thus, with the exception of the of the polypeptide of SEQ ID NO: 2, the skilled artisan cannot envision encompassed variants. Therefore, only a polypeptide of SEQ ID NO: 2, and polypeptides *consisting* of fragments thereof, or polypeptides consisting of fragments thereof and heterologous sequences (e.g. carrier or tag sequences), but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicant's previous arguments regarding the "mature" form of the protein do not appear to be applicable to this new ground of rejection.

Conclusion

Please note the new official fax number below:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-

Art Unit: 1646

5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.


Official papers filed by fax should be directed to (703) 872-9306. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB



9/11/03



YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600